AMENDMENTS TO THE CLAIMS

Listing of Claims

Claims 1.-3. (Canceled).

4. (Previously Presented) A functional G protein biosensor comprising a mammalian α subunit comprising a first amino acid sequence encoding at least one of a first fluorescent or a luminescent protein, and a mammalian $\beta\gamma$ subunit complex, wherein the β subunit comprises a second amino acid sequence encoding at least one of a second fluorescent or luminescent protein and the γ subunit comprise a third amino acid sequence encoding at least one of a third fluorescent or luminescent protein, wherein said first, second and third fluorescent or luminescent proteins are at least FRET or BRET capable.

5. (Canceled).

6. (Canceled).

7. (Previously Presented) A screening method for screening natural or chemically synthesized candidate agonists and antagonists that bind to previously characterized, uncharacterized or "orphan" mammalian receptors, said method comprising exposing an intact living cell containing said receptors and the G protein biosensor of Claim 4 to the candidate agonists and antagonists, wherein the fluorescent protein tagged mammalian G protein α and $\beta\gamma$ subunit complex when reactively exposed to the candidate agonists elicits a decrease in FRET signal and when subsequently exposed to an antagonist results in an increase in the FRET or BRET signal; measuring the FRET signal and/or BRET signal to identify candidate agonist(s) and antagonist(s) for said characterized, uncharacterized or orphan receptor.

8. (Canceled).

9. (Previously Presented) A method for determining signal transduction activity in a live mammalian cell system using FRET analysis, which comprises exposing a biosensor cell comprising a mammalian G protein coupled receptor and the G protein biosensor of Claim 4 to agonists and antagonists and quantifiably measuring G protein receptor signaling activity non-invasively in an intact mammalian cell.

10. (Canceled).

11. (Previously Presented) A non-invasive method for identifying a candidate therapeutic drug molecule, which comprises obtaining a FRET output as a profile over a time period by exposing a live biosensor cell comprising the G protein biosensor of Claim 4 to a candidate therapeutic drug molecule, wherein said first, said second and said third fluorescent or luminescent proteins are expressed in cells containing a receptor or an orphan receptor (a) in the absence of the added candidate therapeutic drug molecule; (b) in the presence of the added candidate therapeutic drug molecule; and comparing said FRET profile (b) with said FRET profile (a) to obtain a comparison of the FRET profile of (b) with the FRET profile of (a).

12. (Canceled).

13. (Previously Presented) A method in accordance with Claim 11 wherein if said comparison shows emitted FRET signal intensity after the addition of the candidate therapeutic drug molecule (b) is less than the FRET signal intensity before the addition of the candidate therapeutic drug molecule (a), then one classifies the candidate therapeutic drug molecule as an agonist candidate therapeutic drug molecule, and if the comparison shows that said FRET profile (b) is similar to said FRET profile (a), then one classifies the candidate therapeutic drug molecule as a molecule likely not having agonistic therapeutic value.

14. (Previously Presented) A method in accordance with Claim 13 wherein a number of different candidate therapeutic drug molecules are added to said biosensor containing cells, singly or as a pool of various candidate therapeutic drug molecules and FRET profiles of these

candidate therapeutic drug molecules are obtained to classify candidate therapeutic drug molecules.

15. (Previously Presented) A non-invasive screening method for identifying agonist candidate therapeutic drug molecules comprising exposing an intact live biosensor cell system containing a receptor and the G protein biosensor of Claim 4 to a candidate therapeutic drug molecule and measuring the reduction of the intensity of said FRET signal which indicates that said candidate therapeutic drug molecule is an agonist therapeutic drug molecule.

16. (Canceled).

17. (Previously Presented) A non-invasive screening method for identifying antagonistic activity of a candidate therapeutic drug molecule comprising exposing an intact live biosensor cell system containing a receptor and the G protein biosensor of Claim 4 to a known agonist and subsequently to a candidate therapeutic drug molecule, said agonist being capable of binding to the receptor, measuring the reduction of an emitted FRET signal, measuring the increase in the intensity of the FRET signal after subsequent binding of the candidate therapeutic drug molecule, and comparing the intensity of the FRET signal subsequent to the addition of the said agonist alone to the FRET signal after binding of the candidate therapeutic drug molecule, which indicates that the candidate therapeutic drug molecule is a therapeutic antagonist molecule.

18. (Canceled).

19. (Previously Presented) A non-invasive screening method for identifying natural or chemically synthesized candidate agonists and antagonists that bind to uncharacterized or "orphan" mammalian receptors thus de-orphaning orphan receptors, said method comprising exposing an intact living biosensor cell containing the orphan receptor and the G protein biosensor of Claim 4 to the candidate agonists and antagonists, measuring a decrease in an emitted FRET signal when the fluorescent protein tagged mammalian G protein α subunit and $\beta\gamma$ complex subunit are reactively exposed to the candidate agonists when agonists bind to the

receptor, measuring an increase of the FRET signal when the same receptor subsequently contacts an antagonist, and identifying candidate agonist(s) and antagonist(s) for the said orphan receptor.

20. (Original) A method in accordance with Claim 19 wherein said method further comprises adding to the biosensor containing cells, a molecule known as an agonist to provide a FRET profile (c) and subsequently adding to biosensor a candidate therapeutic drug molecule which provides FRET profile (d) and comparing the FRET profile (d) with the FRET profile (c).

21. (Canceled).

22. (Previously Presented) A method in accordance with Claim 19 wherein if the FRET signal after the addition of a candidate therapeutic drug molecule in FRET profile (d) is greater than the intensity of the FRET signal after the addition of the known agonist in profile (c), then one classifies the molecule added second as an antagonist candidate therapeutic drug molecule.

23. (Previously Presented) A method in accordance with Claim 19 wherein if the FRET signal after the addition of a candidate therapeutic drug molecule in FRET profile (d) does not alter the FRET profile (c), then one classifies the added candidate therapeutic drug molecule is not an antagonist.

24. (Previously Presented) A method in accordance with Claim 19 wherein one or a number of different molecules are added to the biosensor containing cells, singly or as a pool of various candidate therapeutic drug molecules and FRET profiles of these candidate molecules are obtained to classify candidate therapeutic molecules.

25. (Withdrawn) A method for identifying a candidate therapeutic molecule as an inverse agonist by obtaining a FRET profile of a biosensor cell in accordance with Claim 1 containing overexpressed or mutant receptors of defined or orphan status possessing constitutive

activity such that the FRET profile (e) is lower than FRET profile (a) from the biosensor cells expressing the same receptor without constitutive activity.

26. (Withdrawn) A method in accordance with Claim 25 for classifying a candidate molecule as an inverse agonist, wherein the cells that exhibit a profile (e) are exposed to candidate molecules and the resulting FRET profile (f) is compared with FRET profile (e).

27. (Withdrawn) A method in accordance with Claim 25 wherein if the FRET signal intensity is increased after addition of the candidate in profile (f) compared to the intensity of the signal in FRET profile (e), then the added molecule is classified as an inverse agonist candidate therapeutic drug molecule.

28. (Withdrawn) A method in accordance with Claim 25 wherein if addition of the candidate does not alter the FRET profile (e), then the added molecule is classified as not likely an inverse agonist.

29. (Withdrawn) A method in accordance with Claim 25 wherein a number of different molecules are added to the biosensor containing cells, singly or as a pool of various candidate molecules and FRET profiles of these candidate molecules are obtained to classify candidate therapeutic molecules.

30. (Withdrawn) A method in accordance with Claim 25 comprising an in vitro method comprising obtaining FRET profiles of partially or fully purified biosensor in the presence of partially or fully purified receptor protein of defined or orphan status and making comparisons of said FRET profiles with baseline FRET profiles.

31. (Previously Presented) A classification method for natural or chemically synthesized candidate agonists, antagonists and inverse agonist that bind to previously characterized, uncharacterized or "orphan" mammalian receptors, said method comprising exposing an intact living insect cell wherein the G protein biosensor of Claim 4 as well as receptors are expressed

using a baculovirus vector to candidate therapeutic drug molecules, obtaining a FRET profile therefrom in the presence or absence of the candidate therapeutic drug molecules and comparing these obtained FRET profiles to identify agonists, antagonists and inverse agonists for the receptors.

32. (Withdrawn) A method for increasing the number of receptor types that will couple to the biosensor by mutationally altering the C terminal tail of the alpha subunit constituent of the biosensor.

33. (Withdrawn) A method for altering the intensity of the FRET response from G proteins designed as biosensors by mutationally altering the intrinsic biochemical properties of the subunits that constitute the biosensor.

34. (Withdrawn) A method for altering the intensity of the response seen in the FRET profile to agonist, antagonist and inverse agonist molecules by mutationally introducing pertussis toxin insensitivity into the biosensor of Claim 1 and/or reducing the concentration of endogenous G protein subunits in cells containing the biosensor.

35. (Previously Presented) The functional G protein biosensor of claim 4, wherein the first, second and third fluorescent or luminescent proteins are FRET capable and the addition of an agonist for the G protein coupled receptor reduces the FRET signal intensity from the biosensor.

36. (Canceled).

37. (Previously Presented) A method of classifying candidate therapeutic molecules as agonists, antagonists or inverse agonist comprising exposing receptor-G protein biosensor cells comprising the G protein biosensor of Claim 4 to candidate therapeutic molecules, wherein the receptor-G protein biosensor cells express the fluorescent protein tagged α subunit tethered to a G protein coupled receptor and the fluorescent protein tagged $\beta\gamma$ complex and screening for

predicted changes in the FRET profile from these cells in response to the addition of the candidate therapeutic molecules by quantifiably measuring G protein receptor signaling activity non-invasively in an intact mammalian cell.

38. (Previously Presented) A live functional G protein biosensor cell comprising the G protein biosensor of Claim 4.

39. (Currently Amended) A method for identifying and classifying multiple candidate therapeutic molecules comprising exposing the same G protein biosensor cell comprising the G protein biosensor of Claim 4 to agonistic and antagonistic compounds by repetitive treatment, wherein the fluorescent protein tagged mammalian G protein α and $\beta\gamma$ subunit complex when reactively exposed to the agonistic compound elicits a decrease in FRET signal and when subsequently exposed to the antagonist compound results in an increase in the FRET or BRET signal; measuring the FRET and/or BRET signal; and analyzing FRET and/or BRET signal, thereby identifying and classifying the multiple candidate therapeutic molecules.

40. (Currently Amended) A method for identifying and classifying a single candidate therapeutic molecule by exposing the same G protein biosensor cell comprising the G protein biosensor of Claim 4 to agonistic and antagonistic compounds by repetitive treatment, wherein the fluorescent protein tagged mammalian G protein α and $\beta\gamma$ subunit complex when reactively exposed to the agonistic compound elicits a decrease in FRET signal and when subsequently exposed to the antagonist compound results in an increase in the FRET or BRET signal; measuring the FRET and/or BRET signal; and analyzing FRET and/or BRET signal, thereby identifying and classifying the candidate therapeutic molecule.

41. (Withdrawn) A live functional biosensor cell or biosensor comprising a mammalian alpha subunit in which its carboxyl-terminal domain has been substituted with the corresponding domain of another α subunit with a distinctly different receptor specificity such that the biosensor cell can be used for screening for therapeutic molecules that are agonists, antagonists or inverse agonists of different receptor types.

42. (Withdrawn) A live functional biosensor cell or biosensor containing mutant forms of the G protein sensor that alter the receptor coupling capability of the G protein such that it can be used for identifying and classifying therapeutic molecules which are agonists, antagonists or inverse agonists of various receptor types.

43.-45. (Canceled).